

125259 Mid-Cycle Review Meeting Summary on CMC:

Introduction: Cervarix is a bivalent, HPV vaccine that contains virus-like particles (VLPs) made from the L1 protein of HPV 16 and HPV 18. The L1 proteins are expressed in -----(b)(4)----- cells after inoculation with recombinant baculoviruses containing the open reading frame of a type-specific, C-terminally truncated L1 protein.

The HPV-16 L1 VLP and HPV-18 L1 VLP antigen production process (drug substance) can be divided into -(b)(4)- separate stages. These include:

------(b)(4)-----

The Cervarix final drug product formulation and filling process includes:

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- Transfer final bulk product to filling area
- Fill product into single dose vials or syringes
- Perform final container quality control testing
- Transfer final filled containers for storage/packaging/distribution

Figures 2 and 3 below include process flow diagrams for the production of monovalent adsorbed bulks, figure 2, and the formulation and filling of final drug product, figure 3.

Robin Levis, PhD – July 23, 2007

One (1) Page Determined to be Non-Releasable: (b)(4)

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CMC review comments to date:

Preclinical immunogenicity This data was reviewed under the IND. Information was also submitted to the BLA. The critical pre-clinical studies that were conducted compared the use of vaccine formulated with AS04 adjuvant, vaccine formulated with aluminum hydroxide adjuvant, or vaccine formulated with no adjuvant. Based on all immune parameters studied, vaccine containing AS04 gave the best results. No additional questions remain concerning the preclinical studies performed to support the use of the AS04 adjuvant for this vaccine formulation, with regards to the immunogenicity profile of the vaccine. *It is important to note that while these studies*

measured reactogenicity at injection site and the overall health of the animals, these were not toxicity studies.

I believe that we have reviewed most of the studies related to the identification of this feature and the characterization of the cell line containing this feature under the IND. I would like to request if there are any additional ongoing studies being performed on this feature.

Besides the presence of this unknown structure in the cell line, the cells have been well characterized and there are no further questions regarding the cell substrate at this time.

Materials of animal origin No serum is used in manufacturing process. The only material of animal origin used in the manufacturing process of the HPV vaccine is -----(b)(4)----- that are used to make complete ---(b)(4)--- used to produce the MPL immunostimulant (b)(4) -----(b)(4)----- are derived from -----(b)(4)----- . The countries of origin of the -(b)(4)- are -----(b)(4)----- . -(b)(4)- by products are not currently thought to pose a risk for TSE and the sources of -----(b)(4)----- from TSE acceptable countries minimizes the risk of transmitting animal spongiform encephalopathy agents.

Manufacturing process development The sponsor has made several changes in the manufacturing process during the clinical testing of the product. Table 2 from section 3.2.P.2.3, Manufacturing modifications during the vaccine development, summarizes the changes made in the process, which clinical study material from each process step was used in and what developmental and commercial scale lots were used for each clinical trial.

Table 2 Manufacturing modifications during the vaccine development

Steps	Process 1	Process 2	Process 3	Process 4
Clinical studies	HPV-001/007	HPV-008, HPV-012, HPV-013	HPV-012, HPV-014, HPV-016	HPV-015, HPV-016
Clinical Phase	IIb	III	III	III
Development Lots	(b)(4)			
Commercial lots				
Formulation				
Antigen production Process				
(b)(4)				

The sponsor conducted a series of studies to demonstrate the comparability of materials made using each of the 4 manufacturing processes described above. The first set of studies was done to show comparability between materials made using processes 1 to 4. The comparability of these processes was demonstrated by evaluating the physico-chemical, immunological and stability properties of materials made using each process. All results showed a high level of comparability between all lots tested. The second set of studies done was to show comparability between process 4 developmental lots and commercial scale vaccine materials. These processes were also compared according to their physico-chemical, immunological and stability properties. All results showed a high level of comparability between process 4 materials manufactured at the developmental scale vs. the commercial scale. ***Based on the results of these manufacturing process comparability studies, I believe that it is okay to accept stability and product characterization data from all materials made from each of the processes.***

The sponsor has two facilities dedicated to the manufacture of Cervarix made using the final commercial process. One facility is for final lots for the US and non-US markets and the second is for final product lots for the non-US market. ***Is there any difference in the product intended for the non-US market?***

Manufacturing Process – bulk drug substance The BLA includes a general description of the manufacturing process and process controls. Missing from the BLA are detailed descriptions of the process steps. The BLA refers to GSK Bio monographs that contain these details. *I would like to request GSK bio monograph #s 4412 and 4409, which describe the preparation of the HPV-16 inoculum and the production of HPV – 16 antigen purified bulk, respectively.*

Manufacturing Process – final drug product The first step of final drug product manufacture is the production of adsorbed monovalent bulks. This process is described in GSK bio monograph #4413 for HPV 16 and #4432 for HPV 18. (#3861 describes production of MPL --- (b)(4) --- and #4434 describes MPL adsorbed bulk production.) The BLA states that commercial scale monovalent adsorbed bulk lots will range from --- (b)(4) -----.

I would like to request monographs #4413 and 4432 be submitted to the BLA. (Liz may want to see the MPL specific monographs.) In addition, if I can't find it, I would like an explanation of how the sponsor defined monovalent bulk lot sizes at --- (b)(4) -----.

This seems to be a wide range and not indicative of consistent manufacturing.

Each final drug product lot is formulated by -----(b)(4)-----
------. Commercial scale lots will
range in size from -----(b)(4)------. Section m3.2.P.3.3 section 3 describes the filling
process. A table is included that describes the each of the filling lines and what the
maximum batch size in units and the maximum filling volume/lot. This section also
states that a single final bulk can be used for the filling of up to -(b)(4)- final
container lots. ***How will the volume for each lot be determined? How is final bulk
stored and how will it be***

aliquoted for multiple final lots? What quality controls are in place to ensure the sterility of stored final bulk product?

Adventitious Agents Testing and Viral Clearance Studies – Based on the presence of potential adventitious agents in both cell lines used during product development, the sponsor has conducted extensive studies on identifying potential adventitious agents and on viral clearance. These have been reviewed in detail in the IND and are also presented in the BLA. *There are no issues identified to date with the adventitious agents testing and viral clearance studies conducted for the manufacturing process. In addition, testing proposed for all final bulk material, as detailed in the BLA and as represented in the lot release protocol is adequate.*

Stability testing and Product shelf life – The sponsor is requesting a 36 month shelf life for final container product stored at 2 – 8° C. Table 7, below, details the final container data currently available.

Table 7 Stability of HPV process 1, 2, 3 and 4 vaccine lots

Vaccine production process	HPV-16/-18 L1 VLP AS04 vaccine		
	Lot number	Long-term stability	Accelerated stability
Process 1	(b)(4)	Stable at +2 to +8°C up to 24 months	(b)(4)
		Stable at +2 to +8°C up to 10 months	
Process 2		Stable at +2 to +8°C up to 36 months	
Process 3		Stable at +2 to +8°C up to 24 months	
Process 4		Stable at +2 to +8°C up to 12 months (for 2 lots)	

*Final containers filled in vials

** Final containers filled in syringes

Real time stability data will be available for this time for developmental clinical lots manufactured using process 2. Three commercial scale clinical lots filled in syringes and three lots filled in vials have been put on stability study for 36 months. Data out to twelve months is included in the BLA. In addition to final container product, there are ongoing, long term stability studies for several product intermediates. These include:

----- (b)(4) -----

------(b)(4)-----

Based on all of the requested intermediate hold times, the sponsor would like to have the following timeline for manufacturing and product hold times.

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- Formulated final bulk: -----(b)(4)-----
- Final container product: 36 months at 2 – 8° C.

Based on this information submitted to the BLA, it appears that the sponsor will potentially be storing adsorbed VLPs either as -----(b)(4)-----, formulated bulks, or final container product for -----(b)(4)-----. They have proposed a cumulative, long term stability study that will encompass this entire time line as a post marketing stability commitment; however the study has just begun. I would like to request what sequential data is available for any of the developmental lots on stability study. We need to determine if this data will support requested product shelf life.

Final Product Lot Release A draft copy of the bulk product release protocol and the final container release protocols are included in the BLA. A separate protocol will be used to release monovalent bulks and MPL as these bulks will potentially be used for multiple final container lots. Review of final container testing and release specifications is still underway and discussions have been initiated with DPQ to create a final container testing plan.

It is my opinion that both protocols have included all appropriate bulk and final container tests. It is also my opinion that no post-licensure final container testing is required for this product.

I have one questions regarding the specifications for the completeness of adsorption (COA) test and for the endotoxin test:

- 1. The specification for COA for bulk product is -(b)(4)- and -(b)(4)- for final product. Please explain the differences in these specifications.*

Sections of the BLA still under initial review The following sections of the BLA are still under initial review. I have some questions for the sponsor related to these sections, but need to finalize my initial review of these prior to commenting. The sections still under initial review include:

- Details of Product characterization tests
- In process quality control testing
- Validation of QC test procedures
- Bulk and final container release specifications